PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Michael S. Brown, et al.	Group Art Unit: Unknown
Serial No.: Unknown	Examiner: Unknown
Filed: Concurrently Herewith	Atty. Dkt. No.: UTSD:249USC2/PAR
For: METHODS AND COMPOSITIONS FOR INHIBITING FARNESYL TRANSFERASE ENZYME	

CERTIFICATE OF EXPRESS MAIL

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Signature

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

In The Specification

At page 2, line 1, insert the following:

25136087.1

--This is a continuation of co-pending application Serial No. 07/937,893, filed December 22, 1992, which is US nationalization of PCT application PCT/US91/02650, filed April 18, 1991, which PCT application is a continuation-in-part of application Serial No. 07/615,715, filed November 20, 1990, now U.S. Patent No. 5,141,851, which is a continuation-in-part of application Serial No. 07/510,706, filed April 18, 1990, abandoned.—

Please amend the title to read: -- METHODS AND COMPOSITIONS FOR INHIBITING FARNESYL TRANSFERASE ENZYME --.

In the Claims

Cancel claims 1-36, 43 and 45-50, without prejudice.

Please rewrite claim 37, 38, 44 as follows:

37. (Once Amended) A method for determining the ability of a candidate substance to inhibit a farnesyl transferase enzyme, comprising the steps of:

(a) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(b) admixing a candidate substance with the enzyme composition;

(c) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to a farnesyl acceptor substrate in the presence of the candidate substance; and

(d) administering the candidate substance to a cancer patient to determine the ability of the candidate substance to treat or palliate the cancer.

38. (Once Amended) The method of claim 37, wherein the farnesyl transferase composition comprises a purified farnesyl:protein transferase enzyme, characterized as follows:

(a) capable of catalyzing the transfer of farnesol to a protein or peptide having a farnesyl acceptor moiety;

(b) capable of binding to an affinity chromatography medium comprised of TKCVIM coupled to a suitable matrix;

(c) exhibiting a molecular weight of between about 70,000 kDa and about 100,000 kDa upon gel filtration chromatography, and comprised of two different subunits, each exhibiting a molecular weight of approximately 45,000 kDa to 50,000 kDa upon SDS-PAGE; and

(d) having a farnesyl transferase activity that is capable of being inhibited by TKCVIM; CVIM; or KKSKTKCVIM.

44. (Once Amended) A method of inhibiting the attachment of a farnesyl moiety to a *ras* protein in malignant cells comprising contacting said cells with an effective concentration of a farnesyl transferase inhibitor that inhibits the farnesylation of p21ras by farnesyl transferase enzyme, where the farnesyl transferase inhibitor has been prepared by a process comprising:

(a) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(b) admixing the substance with the enzyme composition;

(c) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to the farnesyl acceptor substrate in the presence of the substance; and

(d) selecting a substance found to have the ability to inhibit the transfer of the moiety to the substrate.

Please add the following new claims, claims 51 - 53:

51. A method of inhibiting the attachment of a farnesyl moiety to a ras protein in malignant cells comprising contacting said cells with an effective concentration of a farnesyl transferase inhibitor that inhibits the farnesylation of p21ras by farnesyl transferase enzyme, the farnesyl transferase inhibitor being an inhibitor that was previously determined to have farnesyl transferase inhibitory activity through testing in the presence of farnseyl transferase enzyme *in vitro*, wherein the farnesyl transferase inhibitor has been prepared by a process comprising:

(a) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(b) admixing the substance with the enzyme composition;

(c) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to the farnesyl acceptor substrate in the presence of the substance; and

(d) selecting a substance found to have the ability to inhibit the transfer of the moiety to the substrate.

52. A method of determining the ability of a substance to inhibit farnesyl transferase enzyme in cancer cells having a ras-related malignancy, the method comprising:

(a) selecting a substance suspected of having the ability to inhibit farnesyl transferase enzyme by a method that includes:

(i) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(ii) admixing the substance with the enzyme composition;

(iii) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to the farnesyl acceptor substrate in the presence of the substance; and

(iv) selecting a substance found to have the ability to inhibit the transfer of the moiety to the substrate; and

(b) determining the ability of the substance to inhibit farnesyl transferase enzyme in malignant cells of a patient having a ras-related cancer.

53. A farnesyl transferase inhibitor prepared by a process comprising selecting a substance suspected of having the ability to inhibit farnesyl transferase enzyme by a method that includes:

(a) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(b) admixing the substance with the enzyme composition;

(c) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to the farnesyl acceptor substrate in the presence of the substance; and

(d) selecting a substance found to have the ability to inhibit the transfer of the moiety to the substrate.

REMARKS

I. The Present Case

The active claims in this case are claims 37-42, 44 and 51-53, which, with the exception of new claim 53, constitute the Group V claims from the earlier restriction requirements (copies enclosed).

The specification has been amended to recite the relationship with the parent cases, Serial No. 07/937,893, filed December 22, 1992 (US nationalization of PCT application PCT/US91/02650, filed April 18, 1991), which is a continuation-in-part of application Serial No. 07/615,715, filed November 20, 1990, now U.S. Patent No. 5,141,851, which is a continuation-in-part of application Serial No. 07/510,706, filed April 18, 1990, abandoned.

It should be noted that Applicants have filed and amended specification that was amended over the parent PCT application to bring it into conformity with US practice by adding references to the various sections. The present application is based upon a PCT application which did not follow the usual US practice in this regard.

Applicants have also enclosed the various Information Disclosure Statements, PTO Form 1449s and the Sequence Listing filed in the parent case, for the Examiner's convenience. The Examiner is requested to employ the references from the parent case. Should additional copies be required, The Examiner is requested to contact the undersigned.

It is believed that no additional fees are due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Assistant Commissioner is authorized to deduct said fees from Fulbright & Jaworski Deposit Account No. 50-1212/UTSD:249USC2; #10111941/PAR.

II. Status of '893 Parent Case

The present case is a continuation of the parent '893 case, which was filed to proceed with the Group V invention, directed generally to a method of inhibiting an enzyme. The '893 case is currently involved in Interference No. 103,586, with US patent 5,185,248 (Barbacid et al.). A Final Decision has recently been handed down by the Board of Patent Appeals and Interferences awarding priority of the count at issue there to Barbacid *et al.* The count in that case was consistent with cancelled claim 37, which was a Group V invention. That decision was appealed to the Court of Appeals for the Federal Circuit. The CAFC has recently vacated and remanded the matter to the Board of Appeals. *Brown v. Barbacid*, ___ F.3d ___, Appeal No. 00-1590, Interference No. 103,586 (Fed. Cir. 2002) (copy enclosed).

Applicants would be pleased to provide the current Examiner with any information from the ongoing interference.

Respectfully submitted,

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Date: February 27, 2002

CLAIM AMENDMENTS

37. (Once Amended) A method for determining the ability of a candidate substance to inhibit a farnesyl transferase enzyme, comprising the steps of:

(a) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(b) admixing a candidate substance with the enzyme composition; ~~and~~

(c) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to a farnesyl acceptor substrate in the presence of the candidate substance; and

(d) administering the candidate substance to a cancer patient to determine the ability of the candidate substance to treat or palliate the cancer.

38. (Once Amended) The method of claim 37, wherein the farnesyl transferase composition comprises ~~the composition of claim 1.~~a purified farnesyl:protein transferase enzyme, characterized as follows:

(a) capable of catalyzing the transfer of farnesol to a protein or peptide having a farnesyl acceptor moiety;

(b) capable of binding to an affinity chromatography medium comprised of TKCVIM coupled to a suitable matrix;

(c) exhibiting a molecular weight of between about 70,000 kDa and about 100,000 kDa upon gel filtration chromatography, and comprised of two different subunits, each exhibiting a molecular weight of approximately 45,000 kDa to 50,000 kDa upon SDS-PAGE; and

(d) having a farnesyl transferase activity that is capable of being inhibited by TKCVIM; CVIM; or KKSKTKCVIM.

39. The method of claim 37, wherein the farnesyl acceptor substrate comprises a $p21^{ras}$, or any peptide containing a cysteine at the fourth position from the carboxyl terminus.

40. The method of claim 37, wherein step (c) comprises determining the ability of the candidate substance to inhibit the transfer of farnesyl from farnesyl pyrophosphate to the acceptor substrate.

41. The method of claim 37, wherein the farnesyl moiety is labeled.

42. The method of claim 41, wherein the farnesyl moiety is radiolabeled.

~~43. A method of inhibiting a farnesyl transferase enzyme comprising subjecting the enzyme to an effective concentration of a farnesyl transferase inhibitor in accordance with claim 21, or a candidate substance identified in accordance with the method of claim 29 to be such an inhibitor.~~

44. A method of inhibiting the attachment of a farnesyl moiety to a *ras* protein in malignant cells comprising ~~subjecting~~ contacting said cells ~~to~~ with an effective concentration of a farnesyl transferase inhibitor that inhibits the farnesylation of p21ras by farnesyl transferase enzyme, where the farnesyl transferase inhibitor has been prepared by a process comprising~~in accordance with claim 21, or a candidate substance identified in accordance with the method of claim 29 to be such an inhibitor~~:

(a) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(b) admixing the substance with the enzyme composition;

(c) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to the farnesyl acceptor substrate in the presence of the substance; and

(d) selecting a substance found to have the ability to inhibit the transfer of the moiety to the substrate.

51. A method of inhibiting the attachment of a farnesyl moiety to a ras protein in malignant cells comprising contacting said cells with an effective concentration of a farnesyl transferase inhibitor that inhibits the farnesylation of p21ras by farnesyl transferase enzyme, the farnesyl transferase inhibitor being an inhibitor that was previously determined to have farnesyl transferase inhibitory activity through testing in the presence of farnseyl transferase enzyme *in vitro*, wherein the farnesyl transferase inhibitor has been prepared by a process comprising:

(a) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(b) admixing the substance with the enzyme composition;

(c) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to the farnesyl acceptor substrate in the presence of the substance; and

(d) selecting a substance found to have the ability to inhibit the transfer of the moiety to the substrate.

52. A method of determining the ability of a substance to inhibit farnesyl transferase enzyme in cancer cells having a ras-related malignancy, the method comprising:

(a) selecting a substance suspected of having the ability to inhibit farnesyl transferase enzyme by a method that includes:

(i) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(ii) admixing the substance with the enzyme composition;

(iii) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to the farnesyl acceptor substrate in the presence of the substance; and

(iv) selecting a substance found to have the ability to inhibit the transfer of the moiety to the substrate; and

(b) determining the ability of the substance to inhibit farnesyl transferase enzyme in malignant cells of a patient having a ras-related cancer.

53. A farnesyl transferase inhibitor prepared by a process comprising selecting a substance suspected of having the ability to inhibit farnesyl transferase enzyme by a method that includes:

(a) obtaining an enzyme composition comprising a farnesyl transferase enzyme that is capable of transferring a farnesyl moiety to a farnesyl acceptor substance;

(b) admixing the substance with the enzyme composition;

(c) determining the ability of the farnesyl transferase enzyme to transfer a farnesyl moiety to the farnesyl acceptor substrate in the presence of the substance; and

(d) selecting a substance found to have the ability to inhibit the transfer of the moiety to the substrate.